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Issue: May 3, 2021

Genprex, Inc. CEO discusses how their "Immunogene Therapy" Drug REQORSA, Modulates Apoptosis

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CEOCFO: ***Mr. Varner, according to the GENPREX, Inc website, you are reprogramming the course of cancer and diabetes. Before we talk about how you are doing that, what attracted you to be both co-founder and head the company?***

Mr. Varner: I originally became associated with Genprex as an investor. I was a practicing lawyer and was familiar with the prior cancer technology that Genprex acquired because I had represented the company that Genprex acquired it from. I thought the technology was really exciting. I knew the inventor personally, and knew he was extremely enthusiastic about its potential and his desire to have it pursued. He was, and still is, an international leader in both lung cancer and gene therapy, so I have a great deal of confidence in him as well. Therefore, I joined Genprex as an investor and continued practicing law.

Several years later, Genprex's CEO contracted cancer and had to withdraw from the company, and unfortunately, he later died. I was asked to join as interim CEO on a part-time basis in 2012 until we found another CEO. It absorbed me! I became completely enamored with the technology and the possibility of bringing a new drug -- particularly a gene therapy -- to lung cancer patients. Lung cancer is a devastating and deadly disease. It kills more people than any other form of cancer. I view it as a real opportunity to accomplish something major in my life. I enjoyed my law practice and I did financially well with it, but as I became absorbed by Genprex, I knew it was just much more meaningful. Consequently, I wound down my law practice and took over at the helm of Genprex more than five years ago.

CEOCFO: ***GENPREX is advancing a very unique gene therapy in cancer. Would you tell us, in layman's terms, how REQORSA™ works - how it is different from other gene therapies and what your plans are to bring this to cancer patients?***

Mr. Varner: REQORSA™ is comprised of a cholesterol molecule (just picture a fatty molecule) that encapsulates a tumor suppressor gene and is injected intravenously into the body. It circulates through the body, attaching to cancer cells wherever they are found. These nanoparticles are taken up into the cancer cells up to 33-fold greater than normal cells. This is shown by biopsies. As the nanoparticles get taken up into tumor cells, they express the tumor suppressor gene proteins that replace or supplement missing or deficient tumor suppressor genes in the cancer.

Many cancers are associated with various tumor suppressor genes, that is the absence or the deficiency of a particular tumor suppressor gene, which may be the cause of the cancer or at least one cause of the cancer. By delivering the replacement genes into the tumors, you can replace the deficient genes and activate the body's own immune defense to fight that cancer.

CEOCFO: *Do we know why it works?*

Mr. Varner: The scientists at the major academic research center where this technology was invented and has been developed for more than 10 years, have identified a number of different ways that it works. They refer to it as a "multi factorial agent" in that it has multiple mechanisms of action. It is known to modulate cell signaling, which is the method by which genes signal cells on how to grow, basically telling them how long to grow and when to die. If cell signaling goes awry, it can lead to cancer. Similarly, cell signaling modulates apoptosis, which is natural cell death. All of our cells are programmed to live a certain life and die and then be replaced. That is the natural continuous cycle in our bodies.

All of our cells are constantly dying and being replaced and if they do not die when they should then that could lead to a tumor. Studies have shown that our drug, REQORSA, modulates apoptosis. Other studies have shown that it also stimulates or modulates the immune system to replace the immune function of patients whose natural immune system is deficient because of the absence of TUSC2, the tumor suppressor gene REQORSA delivers. This is why we refer to REQORSA as an "immunogene therapy" because it really has multiple mechanisms of action, a large part of which is stimulating the immune system.

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CEOCFO: *What are your plans to get this to cancer patients? Where are you now and what are some of the upcoming steps?*

Mr. Varner: We have done two prior clinical trials. We completed a Phase 1 clinical trial using our drug as a monotherapy. We also conducted a Phase 1/2 study using REQORSA in combination with the EGFR inhibitor drug, Tarceva® (erlotinib). In the interim, erlotnib was overtaken in the market by a new AstraZeneca drug, Tagrisso® (osimertinib), which is referred to as a third generation EGFR inhibitor or a later generation EGFR inhibitor. We had filed with the FDA for Fast Track Designation for our gene therapy combined with Tarceva, but during the application process we were allowed to change to Tagrisso, which is a more advanced drug and is now considered the standard-of-care for non-small cell lung cancer (NSCLC) in patients who have an EGFR mutation. The FDA granted us the Fast Track Designation for our combination with Tagrisso based on our earlier data with Tarceva. Having received the Fast Track Designation with Tagrisso, we decided not to enroll further in the Tarceva trial, but to pursue the Tagrisso combination instead. We expect to initiate our Phase 1/2 clinical trial in NSCLC, which we call Acclaim-1, combining REQORSA, our gene therapy, with Tagrisso soon. Therefore, our pathway for approval for REQORSA plus Tagrisso is to complete this upcoming Acclaim-1 clinical trial. The trial was designed such that on the strength of the data, we could potentially file for Breakthrough Therapy status, which if granted, could allow this study to serve as a registrational trial.

Now switching gears and turning to another REQORSA program in NSCLC. Parallel to our study with Tagrisso, we are also pursuing a Phase 1/2 clinical trial of REQORSA in combination with Keytruda®, Merck's checkpoint inhibitor and their largest selling drug, which posted $14 billion in revenue last year. We call this clinical trial Acclaim-2. Our academic collaborators have continued to do preclinical research with our technology and have generated very compelling data showing that REQORSA is synergistic with checkpoint inhibitors, including Keytruda. In fact, the researchers have done numerous studies on the combination of REQORSA and Keytruda, and just this month (April 2021) presented the positive results of one of these preclinical studies at the American Association for Cancer Research's (AACR) annual meeting.

On April 10th they presented two posters at AACR, one of which was focused on the combination of REQORSA with Keytruda and also on the combination of REQORSA with Keytruda and chemotherapy. The data strongly suggest that REQORSA is synergistic with Keytruda, as well as with Keytruda plus chemotherapy. These findings further support pursuing REQORSA in combination with Keytruda in lung cancer. Hence, we have that trial coming soon as well.

Further supporting our development plan is preclinical evidence to suggest that REQORSA may be effective in a range of other cancers. In addition, it suggests that the platform delivery system we are using in REQORSA, which we call the ONCOPREX® Nanoparticle Delivery System, may also be used to deliver other therapeutic genes that may be effective in indications outside of lung cancer. We are exploring those other cancer indications with REQORSA and also the potential for using other genes in our delivery system.

CEOCFO: ***So far, in all of the work that GENPREX has done, what have you learned that may have surprised you, as well as encouraged you?***

Mr. Varner: That is a very interesting question! I think that perhaps at the very beginning I was surprised by the complexity and difficulty of cancer, specifically with some of the particularly difficult cancers, such as lung cancer. I was surprised at how long researchers have been working on these diseases and how much money has been spent worldwide with modest progress. For example, in lung cancer, the survival rates really have not changed very much in 25 years, despite the introduction of new drugs, such as checkpoint inhibitors and targeted therapies. These are still not curative in late-stage lung cancer. Therefore, there remains tremendous need. That was surprising to me.

I was also surprised, and continue to be surprised, at the deep commitment of many of the cancer researchers to their mission and the depth of scientific research that is done by these very brilliant researchers as they seek to find a cure. I guess one other thing that surprises me is the lack of public resources committed to it. Lung cancer is only one of many cancers, but cancer, in general, kills more than half a million patients each year. The pain and suffering of the patients and their families is tremendous, and cancer bears an enormous economic burden on the healthcare system. Consequently, I thought the government and the public would commit greater resources in the quest to solve it.

CEOCFO: ***In addition to cancer, GENPREX has a program with the University of Pittsburgh to develop a gene therapy in diabetes. Would you tell us a little bit about this technology and how you are working to advance it?***

Mr. Varner: This is a very exciting technology, and we are delighted to have partnered with the very prominent research lab at the University of Pittsburgh led by George K. Gittes, MD and his group. In fact, just this month, we were thrilled to receive the inaugural 'License of the Year' award from the University's Innovation Institute for advances made in our gene therapy program for diabetes. While the data in this program are preclinical, they are very encouraging. Following on compelling mice data, the team is currently conducting research in primates. Gittes and his group recently received a $2.6 million NIH grant to support their research in non-human primates. Once that is completed, and they have a clearly defined dosing and delivery method, then we will move forward toward the clinic. This gene therapy is totally different from our cancer gene therapy, as it uses an AAV (Adeno-Associated Virus) vector to deliver two genes into the pancreas. Those genes convert alpha cells in the pancreas into what the researchers refer to as "beta-like cells" in the pancreas. Of course, beta cells are the ones that produce insulin.

These transformed beta-like cells produced insulin in preclinical research, showing the possibility of eliminating the need for insulin replacement therapy, which many diabetics have to do on a daily basis. So, you can see why this is very exciting! The fact that these are beta-like cells instead of just beta cells is believed to be the reason why they are not destroyed by the immune system. In Type I diabetes, the problem is that the immune system destroys the beta cells that produce insulin, leaving the patient without beta cells. The fact that the immune system does not immediately attack these "beta-like" cells is likely a reason for its success. Again, these data are preclinical but very encouraging. I think the fact that they received this $2.6 million NIH award is great validation, because as you know, an NIH grant of that size is heavily peer reviewed and they are very competitive to receive. Therefore, not only does the funding benefit the research, but I view it as validation to the technology, as well.

CEOCFO: ***Would you tell us a bit about the progress in your manufacturing processes? Why is that so important for you?***

Mr. Varner: It is really tremendously important, and we have accomplished huge company milestones in manufacturing. In gene therapy, manufacturing is one of the biggest challenges. The ability to manufacture a delivery vehicle that effectively carries the gene through the body's various defenses and delivers it into a tumor where it can be effective is very challenging. Many companies and other researchers have developed gene therapies that appear to be promising in the lab, but they have not been able to accomplish large scale manufacturing that would make them viable drugs. In some types of gene therapy, the therapy has to actually be manufactured for each individual patient, which is incredibly expensive, time consuming and difficult for the patients as well, because it requires multiple visits to the clinic and so forth. Therefore, that is a real challenge for many other gene therapy companies.

We have taken the manufacturing that was originally done at an academic research center, and we have been able to transfer the technology out of the academic center, with their assistance, to commercial manufacturers. We have been able to scale the drug so that we can manufacture at large scale. Also, our drug product is shown to be stable, so that it can be stored in cold storage and then shipped for use as needed. The ability to store and ship is key for successful commercialization of a drug, and we have been able to do all of that with our REQORSA gene therapy to date.

With a manufacturing process in place, and due to our unique, proprietary non-viral ONCOPREX delivery system that REQORSA utilizes, we are also able to explore the possibility of delivering many different types of genes. We are able to explore other cancer indications and to conduct research in many locations because of our ability to manufacture our drug in a manner that allows us to ship the drug to many sites. Our manufacturing process enables many possibilities for Genprex, with one of the greatest being production at commercial scale when we potentially receive FDA approval of REQORSA.

CEOCFO: ***Genprex achieved many advancements in 2020. What do you see as the key catalyst in the next 6 to 12 months? Are you funded to support your growth through this period?***

Mr. Varner: Yes. I think catalysts in that period of time are going to be related to our two clinical trials of REQORSA in NSCLC, such as initiating the Acclaim-1 and Acclaim-2 studies, enrolling the patients in the Phase 1 portion of those studies, readouts from the Phase 1 portion of those studies, etc. Switching over to the diabetes program, I think we will have more data out of the University of Pittsburgh that could be very exciting and perhaps more news on moving forward on the diabetes front. Potentially during that period, we could be announcing advances with other gene therapy technologies.

We also have some preclinical programs in early stages that we have not disclosed yet, and we potentially may announce more of those during that period. As far as funding, based on our current operations and planned clinical studies, we have funding to take us into 2024.

CEOCFO: ***It is an exciting time for GENPREX!***

Mr. Varner: Yes, it is! Very much so!